

***Remarks***

***Support for the Amendments***

Support for new claims 46-87 can be found throughout the specification. Specifically, support for new claims 46 and 65 can be found at pages 7-8, paragraph 16; throughout pages 13-15; throughout pages 51-52; at pages 78-79, paragraph 188, at page 101, paragraph 223; throughout pages 147-150; and throughout the Examples and Drawings. Support for new claims 47 and 66 can be found at pages 7-8, paragraph 16 and throughout pages 51-52. Support for new claims 48 and 49 can be found throughout pages 80-81. Support for new claims 50-51 and 67-71 can be found at page 15, paragraph 31, and throughout the Examples and Drawings. Support for new claims 52-53 and 72-73 can be found at page 18, paragraph 35; at page 67, paragraph 160; and throughout pages 80-81. Support for new claims 54-55 can be found throughout pages 147-151. Support for new claims 56-59 and 74-77 can be found at pages 8-9, paragraph 18, and throughout pages 81-86. Support for new claims 60-61 and 78-79 can be found throughout page 46. Support for new claims 62-64 and 80-82 can be found throughout pages 175-177. Support for new claims 83-85 can be found at page 53, paragraph 102; throughout pages 167-175; and throughout pages 184-194. Support for new claims 86 and 87 can be found in claims 12 and 15, respectively, as originally filed; throughout pages 175-177; and throughout the Examples and Drawings. Hence, these amendments do not introduce new matter, and their entry and consideration are respectfully requested.

***Status of the Claims***

By the foregoing amendments, claims 1-45 have been cancelled without prejudice or disclaimer, and new claims 46-87 are sought to be entered. Upon entry of the foregoing amendments, claims 46-87 are pending in the application, with claims 46, 65 and 86 being the independent claims.

***Summary of the Office Action***

In the Office Action dated January 16, 2004, the Examiner has made six rejections of the claims. Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding rejections and that they be withdrawn.

***The Double Patenting Rejection***

In the Office Action at pages 2-3, the Examiner rejected claims 1-11, 13, 14, 44 and 45 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 8, 10 and 12 of Hartley *et al.* (U.S. Patent No. 5,888,732; hereinafter "Hartley") in view of Shuman (document U cited on Form PTO-892 attached to the present Office Action; hereinafter "Shuman"). For reasons unrelated to this rejection, by the foregoing amendments, claims 1-11, 13, 44 and 45 have been cancelled. Thus, this rejection has been rendered moot. However, Applicants respectfully offer the following remarks as to why this rejection should not be applied to new claims 46-87.

The Examiner contends that the ordinarily skilled artisan would have been motivated by the simplicity and ease of the topoisomerase system disclosed in Shuman to make a

variant of the invention disclosed in Hartley by selecting a topoisomerase I as one of the recombinases. Applicants respectfully disagree with this contention.

Present independent claim 46 recites an isolated nucleic acid molecule comprising, in order: (a) at least one first topoisomerase recognition site; (b) at least one first recombination site; (c) at least one nucleic acid segment; (d) at least one second recombination site; and (e) at least one second topoisomerase recognition site, wherein the first topoisomerase recognition site and the first recombination site are separated from each other by about 0 to about 100 nucleotides.

Present independent claim 65 recites an isolated nucleic acid molecule comprising: (a) a first recombination site and a second recombination site; and (b) a topoisomerase recognition site, wherein the first or second recombination site is separated from the topoisomerase recognition site by about 0 to about 100 nucleotides.

Applicants respectfully submit that Hartley, combined with Shuman, does not disclose the subject matter of present claim 46 or present claim 65.

In light of the foregoing remarks, Applicants respectfully submit that Hartley, taken in view of Shuman, is not relevant to the patentability of the presently claimed invention under the judicially created doctrine of obviousness-type double patenting. Hence, this rejection should not be maintained against claims 46-87.

***The Rejection Under 35 U.S.C. § 102(b) over Shuman***

In the Office Action at pages 3-4, the Examiner rejected claims 1-4, 6-11, 13, 14, 44 and 45 under 35 U.S.C. § 102(b) as allegedly being anticipated by Shuman. For reasons unrelated to this rejection, by the foregoing amendments, claims 1-4, 6-11, 13, 14, 44 and

45 have been cancelled. Thus, this rejection has been rendered moot. However, Applicants respectfully offer the following remarks as to why this rejection should not be applied to new claims 46-87. The Examiner contends that Shuman discloses the presently claimed invention. Applicants respectfully disagree with this contention.

Under 35 U.S.C. § 102, a claim can only be anticipated if every element in the claim is expressly or inherently disclosed in a single prior art reference. *See Kalman v. Kimberly Clark Corp.*, 713 F.2d 760, 771 (Fed. Cir. 1983), *cert. denied*, 465 U.S. 1026 (1984); *see also PPG Industries, Inc. v. Guardian Industries Corp.*, 75 F.3d 1558, 1566 (Fed. Cir. 1996) ("[t]o anticipate a claim, a reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter."). The disclosure of Shuman does not meet this burden with respect to claims 46-87.

As noted above, Applicants respectfully submit that Shuman does not disclose the subject matter of present claim 46 or present claim 65.

In view of the foregoing remarks, and in view of *Kalman*, Shuman can not anticipate the present claims, and the rejection under 35 U.S.C. § 102(b) over Shuman should not be maintained against claims 46-87.

***The Rejection Under 35 U.S.C. § 102(b) Over Zechiedrich***

In the Office Action at page 4, the Examiner rejected claims 1-3, 5, 10, 11, 13, 14, 44 and 45 under 35 U.S.C. § 102(b) as allegedly being anticipated by Zechiedrich *et al.* (document V on Form PTO-892 attached to the present Office Action; hereinafter "Zechiedrich"). For reasons unrelated to this rejection, by the foregoing amendments, claims 1-3, 5, 10, 11, 13, 14, 44 and 45 have been cancelled. Thus, this rejection has been

rendered moot. However, Applicants respectfully offer the following remarks as to why this rejection should not be applied to new claims 46-87. The Examiner contends that Zecheidrich discloses the presently claimed invention. Applicants respectfully disagree with this contention.

Applicants respectfully submit that Zechiedrich does not disclose the subject matter of present claim 46 or present claim 65.

In view of the foregoing remarks, and in view of *Kalman*, Zechiedrich can not anticipate the present claims, and the rejection under 35 U.S.C. § 102(b) over Zechiedrich should not be maintained against claims 46-87.

***The Rejection Under 35 U.S.C. § 103(a) Over Hartley and Shuman***

In the Office Action at page 5, the Examiner rejected claims 1-11, 13, 14, 44 and 45 under 35 U.S.C. § 103(a) as being unpatentable over Hartley in view of Shuman. For reasons unrelated to this rejection, by the foregoing amendments, claims 1-11, 13, 14, 44 and 45 have been cancelled. Thus, this rejection has been rendered moot. However, Applicants respectfully offer the following remarks as to why this rejection should not be applied to new claims 46-87.

The Examiner concludes that "[i]t would have been obvious to one of ordinary skill in the art to have modified the 2-recombinase system of Hartley *et al.* by selecting topoisomerase I as one of the recombinases, as taught by Shuman, motivated by the simplicity and ease of the topoisomerase system, as taught by Shuman." Office Action, at page 5, last paragraph. Applicants respectfully disagree with this conclusion.

In proceedings before the Patent and Trademark Office, the examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. *See In re Piasecki*, 223 USPQ 785, 787-88 (Fed. Cir. 1984). The Examiner can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references in such a way as to produce the invention as claimed. *See In re Fine*, 5 USPQ2d 1596,1598 (Fed. Cir. 1988). This burden has not been met by Hartley and Shuman.

As noted above, Hartley, taken in view of Shuman, does not disclose the subject matter of present claim 46 or present claim 65.

In light of the foregoing remarks, Applicants respectfully submit that Hartley taken in view of Shuman does not render the presently claimed invention unpatentable under 35 U.S.C. § 103(a), this rejection should not be maintained against claims 46-87.

***The Rejection Under 35 U.S.C. § 112, First Paragraph***

In the Office Action at page 6, the Examiner rejected claim 5 under 35 U.S.C. § 112, first paragraph, for alleged lack of written description. For reasons unrelated to this rejection, by the foregoing amendments, claim 5 has been cancelled. Thus, this rejection has been rendered moot. However, Applicants respectfully offer the following remarks as to why this rejection should not be applied to new claims 46-87.

The Examiner states that the phrase "mutants, variants and derivatives of the recombination sites of (a), (b), (c), (d), (e), (f), (g), (h) of (i) which retain the ability to undergo recombination," is not described in the specification so as to reasonably convey to

the ordinarily skilled artisan that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner contends that there is not sufficient information set forth in the specification, or available in the prior art, to permit a determination of which mutant recombination sites will retain activity and which will not. The Examiner further contends that it is not apparent that any theory or algorithm exists that would permit the determination of whether a particular sequence holds an active recombination site. Applicants respectfully disagree with these contentions.

The Examiner's attention is directed to the specification at pages 6-7, paragraphs 14-15, where exemplary mutated recombination sites are discussed, and where U.S. Patent Nos. 5,888,732, 6,143,557, 6,171,861, 6,270,969 and 6,277,608, which disclose other mutated recombination sites and methods for determining whether or not such mutants retain activity, are specifically incorporated by reference. Further discussion and non-limiting examples of mutated recombination sites (including several non-limiting examples of mutated *att* and *lox* sites) can be found in the present specification at pages 80-81, paragraphs 190-192, and in U.S. Provisional Patent Application No. 60/136,744, as well as U.S. Application Nos. 09/438,358, 09/517,466, 09/695,065 and 09/732,914, all incorporated by reference in the present specification at pages 80-81. Applicants respectfully note that by incorporating these applications and patents by reference, the contents of these disclosures are considered to be contained in the present specification in their entireties.

The Examiner's attention is also drawn to the Drawings (*e.g.* Figures 16-33) and Examples (*e.g.* Examples 9 and 11), which disclose the use of several mutated recombination sites, including the non-limiting examples of *attB1*, *attB2*, *attP1*, *attP2*, *attL1* and *attL2*, in the practice of the present invention. Applicants respectfully submit that the

ordinarily skilled artisan would readily recognize that any mutant, variant or derivative of a recombination site, including the non-limiting examples described throughout the present specification and the incorporated disclosures, can likewise be used in the practice of the present invention. Applicants therefore submit that the skilled artisan, reading the present specification, would recognize that Applicants were in possession of the presently claimed invention as of the filing date of the present application.

Applicants respectfully submit that the present specification, along with the disclosures specifically incorporated by reference, describe a number of non-limiting examples of mutants, variants and derivatives of recombination sites that retain activity. Furthermore, the patents and applications incorporated into the present specification by reference clearly teach the ordinarily skilled artisan well-known methods and techniques which may be used to determine whether a given mutation, variant or derivative of a recombination site will retain its desired activity for use in the present invention. In view of these disclosures, the ordinarily skilled artisan would readily recognize that Applicants were in possession of the presently claimed invention as of the filing date of the present application.

Based at least in part on the foregoing remarks, Applicants respectfully assert that the present specification fully describes the invention as presently claimed. Applicants respectfully submit that the rejection under 35 U.S.C. § 112, first paragraph, should not be maintained against claims 46-87.



***The Rejections Under 35 U.S.C. § 112, Second Paragraph***

In the Office Action at page 7, the Examiner rejected claims 1-11, 13, 14, 44 and 55, and separately rejected claim 5, under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. For reasons unrelated to this rejection, by the foregoing amendments, claims 1-11, 13, 14, 44 and 55 have been cancelled. Thus, this rejection has been rendered moot.

With regard to the separate rejection of claim 5, Applicants respectfully offer the following remarks as to why this rejection should not be applied to new claims 46-87. The Examiner contends that it is not clear what a mutant, variant or derivative of a recombination site encompasses. Applicants respectfully disagree with this contention.

As discussed above, Applicants submit that the present specification provides sufficient description of the metes and bounds of the mutants, variants and derivatives of recombination sites for use in the present invention. The present specification discloses a number of non-limiting examples of mutants, variants and derivatives, and further provides techniques and methods via which the ordinarily skilled artisan could readily determine which mutants, variants and derivatives of recombination sites fall within the meaning of the claimed invention. Hence, the present claims particularly point out and distinctly claim the subject matter regarding by Applicants as the invention.

In view of the foregoing remarks, Applicants respectfully submit that the rejections under 35 U.S.C. § 112, second paragraph, should not be maintained against claims 46-87.

***Other Matters***

Applicants acknowledge, with gratitude, the allowance of claims 12 and 15. These claims, as originally written, are currently represented as pending claims 86 and 87. Applicants respectfully submit that all pending claims are in condition for allowance.

***Conclusion***

All of the stated grounds of rejection have been properly traversed. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn.

Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

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